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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,070	ZAPPALA, STEPHEN M.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16,17 and 20-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16,17 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14, 16, 17, and 20-25 are pending in this reissue application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 13, 2006 has been entered.

The amendment filed July 13, 2006 proposes amendments to claims 7, 9, 11, 16, 17, and 20 that do not comply with 37 CFR 1.173(b), which sets forth the manner of making amendments in reissue applications. A supplemental paper correctly amending the reissue application is required.

A. Amendments to Claim(s)

For changes to the claims, one must submit a copy of the entire patent claim with the amendments shown by underlining and **bracketing** (strikethrough is not permitted), e.g.,

Amend claim 1 as follows:

Claim 1 (Amended). A pharmacological agent <u>useful</u> for [use as] preemptive analgesia, comprising [a solution comprising] <u>a mixture of a</u> 1% lidocaine [HCL] <u>HCL</u>

solution and a 0.25% bupivacaine [HCL] HCL solution in a ratio less than or equal to 10:1 (volume: volume).

B. Cancellation of Claim(s)

To cancel an original patent claim, in writing, direct cancellation of the patent claim, e.g., Cancel claim 6, or to cancel a new claim (previously added in the reissue), in writing, direct cancellation of the new claim, e.g., Cancel claim 15.

C. Presentation of New Claims

Each new claim (i.e., a claim not found in the patent, that is newly presented in the reissue application) should be presented with underlining throughout the claim, e.g.,

Add claim 21 as follows:

Claim 21. The method of claim 17, wherein said combination comprises epinephrine bitartrate 1:200,000.

Even though original claims may have been canceled, the numbering of the original claims does not change. Accordingly, any added claims are numbered beginning with the number next higher than the number of claims in the original patent. If new claims have been added to the reissue application which are later canceled prior to issuance of the reissue patent, the examiner will renumber any remaining new claims in numerical order to follow the number of claims in the original patent.

D. Amendment of New Claims

An amendment of a "new claim" (i.e., a claim not found in the patent, that was previously presented in the reissue application) must be done by presenting the amended "new claim" containing the amendatory material, and completely underlining

the claim. The presentation cannot contain any bracketing or other indication of what was in the previous version of the claim. This is because all changes in the reissue are made vis- à-vis the original patent, and not in comparison to the prior amendment. Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment. Also, per 37 CFR 1.173(c), each change made in the claim must be accompanied by an explanation of the support in the disclosure of the patent for the change.

E. Amendment of Original Patent Claims More Than Once

The following illustrates proper claim amendment of original patent claims in reissue applications:

A. Patent claim.

Claim 1. A cutting means having a handle portion and a blade portion.

B. Proper first amendment format.

Claim 1 (Amended). A [cutting means] knife having a bone handle portion and a notched blade portion.

C. Proper second amendment format.

Claim 1 (Twice Amended). A [cutting means] knife having a handle portion and a serrated blade portion.

Note that the second amendment must include the changes previously presented in the first amendment, i.e., [cutting means] knife, as well as the new changes

presented in the second amendment, i.e., serrated. The word bone was presented in the first amendment and is now to be deleted in the second amendment. The word "bone" is NOT to be shown in brackets in the second amendment. Rather, the word "bone" is simply omitted from the claim, since "bone" never appeared in the patent. An explanation of the deletion should appear in the remarks. The word notched which was presented in the first amendment is replaced by the word serrated in the second amendment. The word notched is being deleted in the second amendment and did not appear in the patent; accordingly, "notched" is not shown in any form in the claim. The word serrated is being added in the second amendment, and accordingly "serrated" is added to the claim and is underlined. In the second amendment, the deletions of "notched" and "bone" are not changes from the original patent claim text and therefore are not shown in brackets in the second amendment. In both the first and the second amendments, the entire claim is presented only with the changes from the original patent text.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-8 and 16, 17 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seow et al., Miller, Goodman and Gilman and Cousins et al.

The claims are drawn to a compositions and methods of reducing perioperative pain comprising administering lidocaine and bupivacaine and optionally a buffer and a vasoconstrictor in a ratio of less than or equal to 10:1. The agent is capable of providing analgesic effect for at least 6 hours and is administered as an injectable therapy selected from subcutaneous, caudal, epidural, intramuscular, intradural, intraspinous, and peripheral nerve blockade.

Seow et al. teach administration of 2% lidocaine and 0.5% bupivacaine in a mixture for epidural blockade in ratios of from 3:1 to 1:3 which overlaps and encompasses the claimed ranges. Further, regarding the claims ranges of less than 10:1, one skilled in the art would have been motivated to prepare additional useful compositions of the ranges taught by the prior art. While the reference is silent regarding some % ratios, the difference in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. When the general conditions are disclosed in

the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 45, 105 USPQ 233, 235 (CCPA 1955). In the absence of any criticality and/or unexpected results of the additional ranges claimed, instant invention is considered obvious. The anesthetic agents contained 1:200,000 epinephrine (a vasoconstrictor) (see abstract).

Duration of action of the lidocaine and bupivacaine is 286 ± 32 minutes (see Seow abstract). This differs from the claimed "at least 6 hours" however, Goodman and Gilman teaches the duration of action and peak concentrations of local anesthetics in blood depends upon the amount injected, the physical characteristics of the local anesthetic and whether epinephrine is used. They are also determined by the rate of blood flow to the site of injection (page 313, column 1). By adding epinephrine, the duration can be approximately doubled by decreasing the rate of absorption of drug into the blood stream (see page 311, columns 1-2). Further, Goodman and Gilman teaches that Goodman and Gilman teach that the latency of the anesthetic effect of lidocaine injected about the ulnar nerve is 3 minutes, but this value is nearly 15 minutes when the drug is injected about the brachial plexus (page 312, column 2) so it also depends on the site of administration. Goodman and Gilman teach the duration of action of bupivacaine is 400 to 450 minutes and the duration of action of lidocaine is 60 to 120 minutes (page 312, column 2). Thus it would have been obvious to one of ordinary skill in the art to vary the aliquot of lidocaine to bupivacaine and to add or exclude epinephrine to increase or decrease the duration of action of the anesthetic motivated

by the teachings of Goodman and Gilman as described above and in Chapter 15 of the Pharmacologic Basis of Therapeutics.

Seow does not teach the combination of 1% lidocaine and 0.25% bupivicaine, however, Miller discloses that to create an epidural blockade, the "usual concentration" range for lidocaine is 1-2% and the "usual concentration" range for bupivacaine is 0.25% to 0.75% (page 506, table 15-7). It would have been made obvious to one of ordinary skill in art at the time it was made to create a rapid-onset, long acting anesthetic motivated by the teaching of Seow et al. who teach lidocaine-bupivacaine combination and the teachings of Miller wherein the concentrations of lidocaine and bupivacaine are selected from the range of usual concentrations.

Goodman and Gilman further teach that in practice, local anesthetics such as lidocaine, which act rapidly but relatively briefly, are **often** combined with an anesthetic such as bupivacaine, which although slow in onset, has a long duration of action.

Cousins provides the motivation to buffer the anesthetic solution wherein it is disclosed that sodium bicarbonate will increase the pH of the local anesthetic solution, which in turn will increase the amount of the drug in the uncharged base form. Thus the rate of diffusion across the nerve sheath and nerve membranes should be enhanced resulting in a more rapid onset of anesthesia. Sodium bicarbonate was added to bupivacaine resulting in a significant decrease in the latency of brachial plexus blockade and it is reported that the duration of anesthesia was prolonged by increasing the pH of the local anesthetic solution (page 105, column 1, first paragraph). It does not teach the specific buffers sodium hydroxide and hydrochloric acid, however, the net effect would

be the same by the addition of the buffers sodium hydroxide and hydrochloric acid, an increase to the pH to 7.4. Additional motivation is provided for the pH of 7.4 because that is the normal pH of human blood and spinal fluid. It would have been obvious to buffer to a pH of 7.4 motivated by the desire for a faster latency period and longer duration of action as disclosed by Cousins.

2. Claims 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seow et al., Miller, Goodman and Gilman and Cousins as applied to claims 1-8, 16, 17 and 20-25 above, and further in view of Ko et al.

Ko et al. teach a method for reducing perioperative pain by injecting a preemptive analgesic solution before incision, wherein the preemptive analgesic used is a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine (page 875). The preincisional injection technique of Ko is infiltration into the dermis and subcutaneous tissues (page 875, column 2, line 1). Although the concentration of Ko et al. was 1% lidocaine and 0.5% bupivacaine HCl, it is disclosed that there may be an advantage to using a larger volume of more diluted anesthetic agents, by diluting the concentration of local anesthetic agents, greater volumes can be used. Greater volumes would be more effective than smaller volumes of more concentrated agents because a larger tissue area may be anesthetized. It would have been made obvious to one of ordinary skill in art at the time it was made to employ a more dilute solution of bupivacaine in the mixture of lidocaine and bupivacaine. Such a modification would have been motivated by the reasoned expectation of producing an anesthetic composition which is effective

in comprehensively producing preemptive anesthesia to greater areas of tissue in a patient as recited by Ko et al. above.

In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention. This motivation may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. Here, filtered through the knowledge of one skilled in the art, the prior art disclosed that lidocaine is available in a concentration of 1% and bupivacaine is available in a concentration of 0.25% and both are available with epinephrine 1:200,000. It is also disclosed in the prior art that lidocaine has a short duration of action and short latency period and bupivacaine has a longer duration of action and a longer latency period. The prior art teaches that these agents are frequently combined because a shorter latency period and longer duration of action is desired in some surgical procedures. It is further disclosed by the prior art that bupivacaine has a duration of action of about 400 to 450 minutes (at least 6 hours). In addition, by the time of the claimed invention, lidocaine and bupivacaine were well-known and successful local anesthetic agents, and were frequently combined. Accordingly, there was clear motivation to combine the lidocaine and bupivacaine to produce a shorter latency period and longer duration of action.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Arguments

Applicant's arguments filed July 13, 2006 have been fully considered but they are not persuasive. Applicant asserts that the reference used in the rejection is a "medical school textbook and cannot be used in determining the scope and contents of the prior art in the field of analgesia and the composition and use of local anesthetics". In response, the Goodman and Gilman reference is routinely used to assess the state of the art and does not "set the level of ordinary skill in the art at the level of a medical student". The reference above sits on many skilled physicians and pharmacologists desks and it does in the examiner's office, and is regularly referred to in the assessment of the level of ordinary skill in the medical arts.

Regarding assertions that the protestor "cherry-picks" the prior art to find parts of the claimed invention, In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Seow et al. teach administration of 2% lidocaine and 0.5% bupivacaine in a mixture for

epidural blockade in ratios of from 3:1 to 1:3 which overlaps and encompasses the claimed ranges, Ko et al. teach a method for reducing perioperative pain by injecting a preemptive analgesic solution before incision, wherein the preemptive analgesic used is a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine (page 875). The preincisional injection technique of Ko is infiltration into the dermis and subcutaneous tissues (page 875, column 2, line 1). Although the concentration of Ko et al. was 1% lidocaine and 0.5% bupivacaine HCl, it is disclosed that there may be an advantage to using a larger volume of more diluted anesthetic agents, by diluting the concentration of local anesthetic agents, greater volumes can be used. Cousins provides the motivation to buffer the anesthetic solution wherein it is disclosed that sodium bicarbonate will increase the pH of the local anesthetic solution, which in turn will increase the amount of the drug in the uncharged base form. Thus the rate of diffusion across the nerve sheath and nerve membranes should be enhanced resulting in a more rapid onset of anesthesia. Goodman and Gilman further teach that in practice, **local anesthetics such as lidocaine, which act rapidly but relatively briefly, are often combined with an anesthetic such as bupivacaine, which although slow in onset, has a long duration of action.** In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See 35 U.S.C. § 103: "A patent may not be obtained...if the differences between the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art".

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986

Applicant asserts that the combination of Seow with Goodman and Gilman would be given more weight if the teaching of the current edition (9th edition) were used. In response, See 35 U.S.C. § 103: "A patent may not be obtained...if the differences between the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art". Accordingly the Examiner is not persuaded by the Applicant's reliance on post-filing date evidence.

Regarding the argument that the Cousins' reference concludes that "the mixtures do not provide significant advantages" applicant alleges that Cousins fails to provide the motivation to combine its teaching with those of other cited references. The Examiner directs Applicant's attention to Upsher-Smith Laboratories Inc. v. Pamlab LLC, 75 USPQ2d 1213 (CAFC 2005). Upsher-Smith argues that the European Application's discussion of the benefits of adding antioxidants to the compositions actually teaches away from expressly excluding antioxidants. However, "a reference is no less obvious if,

after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an obviousness analysis." Bristol-Myers Squibb Co., 246 F.3d at 1378 (quoting Celeritas Techs., Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361 [47 USPQ2d 1516] (Fed. Cir. 1998)). Consequently, the argument that Cousins concludes that "the mixtures do not provide significant advantages" does not raise an issue of material fact. Again, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant asserts that while the ratio in which the lidocaine and bupivacaine solutions are combined falls within the ratio range of the claimed invention, the concentration of the bupivacaine solution is different in Ko, and thus the final concentration of the local anesthetics are different. Ko et al. is cited to teach the method for reducing perioperative pain by injecting a **preemptive analgesic solution** before incision, wherein the preemptive analgesic used is a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine (page 875). The preincisional injection technique of Ko is infiltration into the dermis and subcutaneous tissues (page 875, column 2, line 1). Although the concentration of Ko et al. was 1% lidocaine and 0.5% bupivacaine HCl, it is disclosed that there may be an advantage to using a larger volume of more diluted anesthetic agents, by diluting the concentration of local anesthetic agents, greater volumes can be used. Greater volumes would be more effective than smaller volumes of more concentrated agents because a larger tissue area may be anesthetized.

One skilled in the art would have been motivated to prepare additional useful compositions of the ranges taught by the prior art. While the reference is silent regarding some % ratios, the difference in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. When the general conditions are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 45, 105 USPQ 233, 235 (CCPA 1955). In the absence of any criticality and/or unexpected results of the additional ranges claimed, the instant invention is considered obvious.

Regarding applicant's arguments regarding the 1% lidocaine HCL solution and a 0.25% bupivacaine HCL solution in the cited ratios, The claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts, thus the 0.5% bupivacaine HCL solution cited in the prior art are not excluded from the instant claims.

Regarding the Declaration from Dr Zapala, the showing did not provide an adequate basis to support a legal conclusion of unobviousness.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Patent Examiner
Art Unit 1614

September 25, 2006

Ardin H. Marschel 9/29/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER